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REVIEW

Perioperative Therapy for Locoregional Nonsmall-Cell Lung Cancer

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Surgical therapy remains the treatment of choice for resectable nonsmall-cell lung cancer (NSCLC). However, the 5-year survival results of surgical therapy is 40–70%, which is far from acceptable. In this report, past results of perioperative therapies were reviewed to identify the future direction of effort in improving the therapy of NSCLC. Two perioperative modes of treatment that may possibly improve postsurgical survival were identified, i.e., neoadjuvant chemotherapy for resectable NSCLC and postoperative specific active immunotherapy. © 1996 Wiley-Liss, Inc.

KEY WORDS: **nonsmall-cell lung cancer, perioperative therapy**

INTRODUCTION

Surgical therapy remains the treatment of choice for most patients with resectable nonsmall-cell lung cancer (NSCLC) [1]. The postsurgical 5-year survival rate of 20–35% was acceptable in 1970s for resectable NSCLC [2]. Although a 5-year survival rate of 40–70% has been reported recently, this apparent improvement in survival may be attributed to better intraoperative staging rather than improved surgical therapy [3,4].

To improve these relatively poor survival results of surgical therapy, we may need to look for additional modes of treatment. For the past 40 years, numerous clinical studies of perioperative therapy were carried out in order to improve the survival results of surgical therapy. We review the results of these past trials to determine the future direction in improving treatment of locoregional NSCLC.

PREOPERATIVE RADIATION THERAPY

In 1956, a group of radiation therapists and surgeons was formed to evaluate the efficacy of preoperative radiation therapy in resectable, as well as locally advanced, lung cancers [5]. A total of 41 patients were studied. Following a course of radiation therapy, 26 patients successfully underwent surgical therapy. In 54% of the patients, the resected primary cancer was histologically free of tumor cells. The mediastinum was also histologically free of metastases in 92%.

Based on the above findings, prospective randomized trials of preoperative radiation therapy were carried out by two separate groups of investigators. One of the studies was done in 1960s by 17 institutions supported by a grant from the National Cancer Institute (Committee for Radiation Therapy Studies) [6].

Approximately 1,000 patients with carcinoma of the lung were entered into two separate but integrated therapeutic trials. One study was for patients with lesions considered operable at the time of diagnosis. The patients were randomly assigned to receive either immediate surgery (278 patients) or preoperative radiotherapy followed by surgery (290 patients). The course of radiation therapy consisted of a minimum of 4,000 rads of supervoltage (1 Mev or more) irradiation over 4 weeks to the primary tumor and mediastinum and in appropriate cases, a supraclavicular dose of 5,000 rads.

The 5-year survival of the patients in the immediate surgery group was 16%, whereas that of the radiotherapy-surgery group was 14%.

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The second group of patients, who were clinically inoperable without radiotherapy (potentially operable patients), received a course of radiotherapy. Following completion, 152 patients were considered suitable for attempted resection of the tumor. The randomization assigned 78 to receive surgery and 74 to receive no surgery.

The 5-year survival of the surgery group was 8% and that of the no-surgery group was 6%.

There was no statistically significant difference in the survival rates of the patients in these two groups. Postoperative mortality between the two groups as not different, but postoperative morbidity, such as bronchopleural fistula, was three times more frequently encountered in the preoperative radiotherapy group. Also, it was reported that the recurrence of cancer, either locally or as distant metastasis, was also similar in the two groups.

Another randomized trial of preoperative radiotherapy was carried out in the 1960s by a group of 23 Veterans Administration Hospitals, the VA Surgical Adjuvant Cancer Chemotherapy Group [7]. A total of 339 patients with operable lung carcinoma were randomized to the preoperative X-ray therapy group versus the thoracotomy-only group. The patients in the preoperative X-ray therapy group received 4,000–5,000 rads 4–6 weeks prior to the thoracotomy. There was no statistically significant difference in survival, postoperative mortality, and morbidity.

Thus the authors concluded that the routine use of preoperative X-ray therapy in lung cancer was contraindicated. Much later in 1980s, Pearson et al. from Toronto [8] stated that preoperative radiotherapy of 4,000 rads in 15 treatments resulted in much higher postoperative morbidity and mortality, compared to no preoperative radiotherapy. Accordingly, their patients were then given radiotherapy postoperatively instead of before the surgery [8].

POSTOPERATIVE RADIOTHERAPY

In the 1970s, a prospective randomized study of postoperative radiotherapy of resectable lung cancer was done by a group of investigators in Belgium [9]. A total of 175 patients were entered into the study. Most of the patients had Stages I and II NSCLC, and the tumor had been completely resected. The patients in the study group received 6,000 rads in 6 weeks using Co60 unit. No increase in survival time was noticed in the irradiated group. The 5-year survival rate was lower (24% vs. 43%) than in the control group. A detrimental effect of radiation therapy was observed in the T_2 group ($P < 0.05$); this was significant especially after pneumonectomy. The 5-year survival rate was 16% vs. 43% for control $P < 0.01$. A slight benefit observed from radiotherapy was a decrease in local relapse (4 vs. 19 patients). The following complications due to the radiotherapy were observed: lung fibrosis, six patients; radiation pneumonitis, one patient; esophageal rupture, one patient; and constrictive pericarditis, one patient.

The authors concluded that it would be unnecessary to use systematic radiotherapy after complete resection of bronchogenic carcinoma without lymph node metastases or extension beyond the lung.

More recently, in 1980s the Lung Cancer Study Group carried out a randomized study of postoperative radiotherapy in Stages II and III epidermoid carcinoma of the lung [10]. A total of 230 patients entered the study. The radiotherapy was delivered by megavoltage equipment (with cobalt-60 or a higher energy source) and directed to the mediastinum, and a dose of 5,000 rads was given.

The log rank comparison of rates of local recurrence showed a significant difference ($P < 0.001$): Only one first recurrence was local in radiotherapy group, as compared with 21 in the control group.

However, data on survival provided no evidence in favor of radiotherapy largely because 75% recurrences were outside the radiation field, and also slight excess of deaths with cancer among control patients was offset by a slight deficit in the deaths without cancer (possible complications from radiotherapy). The authors concluded that significant improvements in the survival of patients with resectable epidermoid carcinoma require more effective systemic therapy.

FAILURE PATTERNS FOLLOWING SURGICAL THERAPY OF NSCLC

In order to improve the survival results of surgical therapy for NSCLC, it is important to find out why and how the surgical therapy would fail. Matthews et al. [11] reviewed the autopsy results of patients with operable NSCLC who died within 30 days following a curative resection.

Of 202 patients, 73 (35%) were found to have residual tumor at the time of autopsy. Of 73 patients, one-third had residual local disease and two-thirds had distant metastases. The most frequent sites of distant metastases were adrenal glands, liver, brain, and lymph nodes.

More recently, Feld et al. [12] reviewed the records of 390 patients with resected Stage I NSCLC who were in an adjuvant immunotherapy trial. There were 158 patients with recurrence (40%). In 26%, the site of the first relapse was in the involved lung (local recurrence). In the rest (74%), the first site of relapse was distant, and the most frequent sites were brain, bone, and the contralateral lung. Thus it is very clear that in order to improve the results of surgical therapy, we need to control the recurrence at distant sites.

Postoperative Adjuvant Chemotherapy

Studies on failure patterns following surgical therapy of NSCLC showed that about two-thirds of patients failed due to distant metastasis. Then, it would be most logical

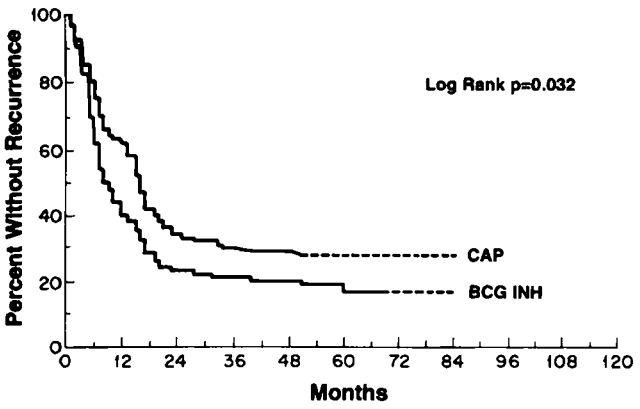

Fig. 1. Kaplan-Meier disease-free survival of 130 patients with completely resected adenocarcinoma or large cell lung carcinoma treated with chemotherapy (CAP) or immunotherapy (BCG/INH). Used with permission of the Publisher, American College of Chest Physicians. Adapted from Chest, Vol. 103, No. 1, January 1993, "Postoperative Chemotherapy for Non-Small-Cell Lung Cancer," by Holmes [15].

to design adjuvant therapy directed to control distant metastasis, besides the local recurrence. Clinical trials of postoperative adjuvant chemotherapy have been carried out since the late 1950s. A comprehensive review of adjuvant chemotherapy in lung cancer was prepared by Legha et al. and published in 1977 [13].

Major studies reported in 1976 were reviewed. Most of the studies dealt with single agent postoperative chemotherapy, mostly with cyclophosphamide. In summary, none of the clinical trials of postoperative adjuvant chemotherapy with a single agent for lung cancer clearly demonstrated the survival advantage, compared to the no treatment control group.

In mid-1970s, cisplatin was added to the combination chemotherapy for lung cancer, and much improvement in the response rate was noted [14]. The Lung Cancer Study Group in 1977 began a series of clinical trials testing the efficacy of postoperative adjuvant chemotherapy using a combination of cyclophosphamide, doxorubicin, and cisplatin (CAP regimen).

Holmes et al. [15] reported the results of adjuvant chemotherapy in Stages II and III adenocarcinoma and large cell carcinoma. A total of 130 patients with Stage II and Stage III adenocarcinoma and large cell carcinoma, following a complete resection, were randomized to two arms (Fig. 1).

The control arm of patients received intrapleural administration of bacillus Calmette-Guerin (TICE® BCG, 10^{-7}, Organon, West Orange, NJ) [16]. This was followed by p.o. administration of levamisole 2.5 mg/kg, 3 consecutive days, every other week for 18 months. The chemotherapy arm of patients received a 6-month course of cytoxan, 400 mg/m^2, adriamycin, 40 mg/m^2, and cisplatin, 40 mg/m^2. The patients in the chemotherapy group, on the final analysis, received only 58% of the full protocol dosage.

There was significant improvement in the disease-free duration and overall median survival of the patients in the chemotherapy group compared to those of the patients in the control group (~7 months longer than those of the control group).

Then, Lad et al. [17] reported the results of adjuvant chemo-radiotherapy versus radiotherapy in incompletely resected locally advanced nonsmall-cell lung cancers. A total of 164 patients were randomized to two arms of adjuvant therapy. The control arm of patients received 4,000 cGy of radiotherapy in a split-course schedule of 3 weeks interval. The chemotherapy arm of patients received six cycles of CAP (cyclophosphamide 400 mg/m^2, doxorubicin 40 mg/m^2, and cisplatin 40 mg/m^2) together with 4,000 cGy of radiotherapy in a split course.

The median time to recurrence was 8 months for the control (radiotherapy) and 14 months for the chemoradiotherapy arm, and the difference was statistically significant. However, the overall median survival was 13 months for the control and 20 months for the chemo-radiotherapy arm, but the difference was statistically not significant. In the chemo-radiotherapy arm, there was a significant decrease in distant metatasis.

These two trials of postoperative adjuvant chemotherapy using the CAP regimen in locally advanced nonsmall-cell lung cancers demonstrated possible beneficial effects of the chemotherapy in improvement of the survival rate. However, in both trials a treatment control arm was not used. Thus the third trial of adjuvant chemotherapy with CAP by the Lung Cancer Study Group was designed to have a no-treatment control arm [18]. The study was done in 269 patients with Stage I NSCLC (T_1N_1 nd T_2N_0) (Fig. 2). The chemotherapy arm was to receive four courses of CAP (cyclophosphamide 400 mg/m^2, doxorubicin 40 mg/m^2, and cisplatin 60 mg/m^2).

There was no difference in time to recurrence or overall survival between the two groups. The analysis revealed that only 53% of patients in the chemotherapeutic arm received all four cycles of chemotherapy. In 74% of the patients, the site of initial recurrence was at distant sites. On the basis of this trial, postoperative adjuvant therapy with CAP was not recommended for patients with resected Stage I NSCLC.

Ohta et al. [19] of the Japan Clinical Oncology Group randomized 209 patients with Stage III NSCLC following complete resection. The control group received no treatment, and the study group received three courses of chemotherapy with vindesine and cisplatin. Analysis of the study revealed that the patients in the chemotherapy arm for various reasons received only 68% of the planned dosage of chemotherapy. The median survival of the control group was 37 months and that of the chemotherapy group was 31 months. The authors concluded that the

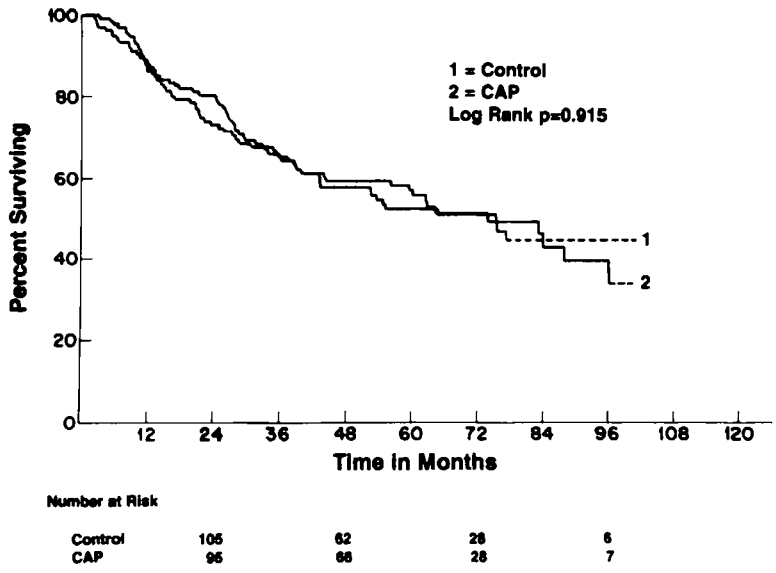

Fig. 2. Time to death (from any cause) by treatment for 269 eligible patients. Used with permission of the Publisher, Journal of the National Cancer Institute. Adapted from JNCI, Vol. 85, No. 4, February 1993, "Adjuvant Chemotherapy With Cyclophosphamide, Doxorubicin, and Cisplatin in Patients With Completely Resected Stage I Non-Small-Cell Lung Cancer," by Feld et al. [18].

relevance for conducting a randomized control study for postoperative adjuvant chemotherapy (specifically for patients who have had resection of NSCLC) in the future remains questionable.

In summary, these randomized trials of postoperative adjuvant chemotherapy did not demonstrate definite advantage in improving the postoperative survival of the patients. One of the most important reasons may be a poor compliance with the planned chemotherapy: only 53%, 58%, and 68% of the patients in the chemotherapy group completed the planned chemotherapeutic courses [15,18,19]. Moreover, it is impossible to observe the response rate of the chemotherapeutic regimen as in all of the patients gross evidence of tumor had been surgically removed.

The reasons for poor compliance with chemotherapy may be physical and psychological. In order to tolerate chemotherapeutic toxicity at least 1 month of recovery time is needed following surgery. This will delay onset of chemotherapy at least 6–8 weeks from the time of initial diagnosis of cancer. Also, after the cancer is removed by the surgery, the patient may feel secure enough to think that further therapy with strong side effects may not be necessary.

PREOPERATIVE CHEMOTHERAPY

The first clinical study of preoperative chemotherapy in locally advanced lung cancer was published in 1979 [20]. A total of 128 patients with unresectable inoperable NSCLC was given combination chemotherapy containing cisplatin. In 43 patients, >50% regression of the lesion was noted (response rate of 34%). Subsequently, in 24 of the 43 patients, surgical resection of the tumor was possible. At the time of the report, 20 patients were alive between 7–33 months. Of the 24 patients, 12 initially presented with distant or supraclavicular node metastases (Stage IIIB or IV). The aims of the preoperative chemotherapy at that time was to make unresectable lung cancers resectable by shrinking the tumor.

In the following decade, numerous Phase II clinical trials of preoperative chemotherapy and/or chemo-radiotherapy for patients with locally advanced (mostly Stage IIIA) NSCLC were reported (Table I) (21–30). The rationale of the preoperative chemotherapy in these trials was to improve the postoperative survival by downstaging the lesion by preoperative chemotherapy.

Surgery for Stage IIIA NSCLC had remained the most controversial area in the surgical management of lung cancer, specially N_2 disease (mediastinal nodal metastases). The 5-year survival rates of surgical therapy alone in Stage IIIA NSCLC, according to the reports, ranged from 0–30% [31]. However, those of radiotherapy are known to be 5–7%, with a median survival of 12 months or less [1].

Some of the trials of preoperative chemotherapy contained concomitant administration of radiation therapy. Eagan et al. [12] (Lung Cancer Study Group) gave two cycles of cyclophosphamide, doxorubicin, and cisplatin together with 3,000 rads of radiotherapy preoperatively. Of 42 patients with Stage IIIA NSCLC, the response rate to the preoperative therapy was 51%. Of the responders, 13 patients had complete surgical resection and the post-

TABLE I. Preoperative Therapy For Stage III Nonsmall-Cell Lung Cancer, Nonrandomized

Investigator	Year	Regimen[a]	Response rate (percent)	Median survival (months)
Takita et al. [21]	1986	P	39	14.5
Eagan et al. [22]	1987	CAP + RT	51	11
Sridhar et al. [23]	1988	FuEP	—	12
Skarin et al. [24]	1989	CAP—RT	72	32.3
Faber et al. [25]	1989	Fu(E)P + RT	—	22
Weiden and Piantadosi [26]	1990	FuP + RT	56	13
Strauss et al. [27]	1992	FuEP + RT	51	15.5
Kirn et al. [28]	1993	P	—	24
Martini et al. [29]	1993	MVP	77	19
Rusch et al. [30]	1993	EP + RT	—	17

[a]P = cisplatin, C = cyclophosphamide, A = doxorubicin, Fu = 5-Fluorouracil, E = etoposide, M = mitomycin, V = vinblastine, RT = radiotherapy.

operative median survival was 15 months. However, the overall median survival of the 42 patients was 11 months.

In 1987, Takita et al. [21] treated 73 patients with Stage III NSCLC; one-half were Stage IIIB. Various cisplatin combination chemotherapy modalities were used. The overall response rate was 39%. The overall median survival was 14.5 months [21].

Sridhar et al. [23] of the Florida group treated 21 patients with Stage III NSCLC. It appears that most of them were unresectable Stage IIIB patients. Two to three cycles of chemotherapy with 5-fluorouracil, etoposide, and cisplatin were given preoperatively. The overall median survival was 52 weeks.

Skarin et al. [24] (Boston) treated 71 patients with marginally resectable Stage III NSCLC. One-half of the patients may have been in Stage IIIB. Two courses of cyclophosphamide, doxorubicin, and cisplatin were followed by a sequential course of radiotherapy of 3,000 cGy. Response rate of 72% was observed. A gross complete surgical resection was possible in 36 patients. The overall median survival was 32.3 months.

Weiden et al. [26] (Lung Cancer Study Group) treated 85 patients with Stages IIIA and minimal IIIB NSCLC. Concomitant use of 5-fluorouracil, cisplatin, and 30 Gy of radiotherapy showed a 56% response rate. In 29 patients complete resection was possible. The overall median survival was 13 months. The authors concluded that "these results suggest a need to define better the relative roles of preoperative radiotherapy and chemotherapy."

Strauss et al. [27] (Cancer and Leukemia Group B, CALGB) treated 41 patients with Stage IIIA NSCLC, the majority with N_2. Patients were treated with concurrent 5-fluorouracil, vinblastine, cisplatin, and 30 Gy of radiotherapy. The response rate was 51%; in 25 patients the lesion was resectable. The overall median survival was 15.5 months. The authors concluded that the median survival seemed to be only modestly improved beyond that achieved with less intensive means of treatment.

Faber et al. [25] (Rush Medical College) treated 85 patients with mostly Stage IIIA NSCLC, concomitant chemotherapy, and 40 Gy of radiotherapy. Chemotherapy consisted of 5-fluorouracil and cisplatin or 5-fluorouracil, etoposide, and cisplatin. Sixty patients subsequently underwent resection. The overall median survival was 22.1 months and that of resected patients was 36.6 months.

Kirn et al. [28] (Boston) treated 60 patients with Stage IIIA (N_2) NSCLC with various cisplatin combinations. Subsequently, 42 patients had a complete resection. The overall median survival was 2 years. In 41% of the patients, the surgical pathological staging showed no evidence of N_2 disease. Thus the authors concluded that the neoadjuvant chemotherapy apparently improved resectability and also pathologically downstaged the IIIA (N_2) disease.

Martini et al. [29] (Memorial Sloan-Kettering Cancer Center) treated 136 patients with Stage IIIA (N_2) NSCLC with mitomycin, vindesine (or vinblastine), and cisplatin. The response rate was 77%, and in 82 patients the lesion was completely resected. The overall median survival was 19 months and that of completely resected patients was 27 months. However, they reported 15 patients with mitomycin toxicity affecting the lung.

Rusch et al. [30] (South Western Oncology Group) treated 51 patients with Stage IIIB NSCLC. The regimen consisted of etoposide, cisplatin, and concurrent radiotherapy of 45 Gy. In 32 patients, the lesion was resected; the overall median survival was 17 months.

Roth et al. [32] (M.D. Anderson) reported results of their prospective randomized clinical trial of Stage IIIA NSCLC. A total of 60 patients were randomized to the surgery-alone group and the perioperative chemotherapy group (Fig. 3). As chemotherapy, cyclophosphamide, etoposide, and cisplatin were given in three cycles preoperatively and in three cycles postoperatively. The median survival of the surgery-alone group was 11 months and that of perioperative chemotherapy group was 64 months

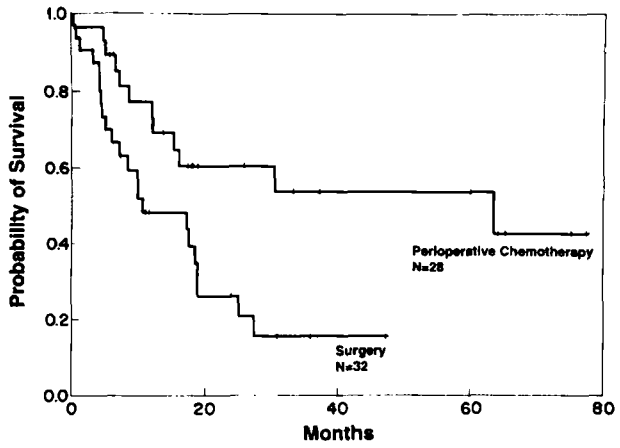

Fig. 3. Time to death (from any cause) by treatment for 60 eligible patients, logrank (P = .008). Used with permission of the Publisher, Journal of the National Cancer Institute. Adapted from JNCI, Vol. 86, No. 9, May 1994, "A Randomized Trial Comparing Perioperative Chemotherapy and Surgery With Surgery Alone in Resectable Stage IIIA Non-Small-Cell Lung Cancer," by Roth et al. [32].

($P = 0.008$). The authors concluded that the patients with resectable Stage IIIA NSCLC should no longer be treated with surgery alone.

Dillman et al. [33] (CALGB) conducted a prospective randomized trial of radiotherapy alone (60 Gy) or induction chemotherapy followed by radiotherapy (60 Gy) in regionally advanced NSCLC. A total of 165 patients were studied. The chemotherapy consisted of two cycles of vinblastine and cisplatin. The median survival of the chemo-radiotherapy group was 13.8 months, compared to 9.7 months for the control.

Le Chevalier et al. [34] (Institute Gustave Roussy) randomized 353 patients to radiotherapy alone (65 Gy) or induction chemotherapy followed by radiotherapy (65 Gy). The median survival of the chemotherapy group was 12 months and that of the control group was 10 months. However, there was significant decrease in incidence of the distant metastasis recurrence of the patients in the chemotherapy group.

Numerous clinical Phase II trials of neoadjuvant chemo(radio)therapy showed possible survival advantage to those who received radiotherapy alone. Roth et al. [32] finally demonstrated a convincing survival advantage of perioperative chemotherapy to that of surgery alone in the treatment of IIIA NSCLC by a prospective randomized study.

Review of the preoperative (or induction) chemotherapies for Stage III NSCLC in Phase II studies revealed the median survival in the majority of reports to be over 12–24 months. One of the investigators, however, reported a median survival of 32.3 months, which is much superior to the others.

In this series the radiotherapy was given sequentially following the chemotherapy. It is speculated that sequentially given chemotherapy and radiotherapy may work in synergistic fashion.

However, when chemo-radiotherapy is given concomitantly, reduction in dosage of both modalities may be necessary to avoid strong side effects. Another consideration is that in case of concomitant chemoradiotherapy, the chemotherapy may be acting as a radiosensitizer, rather than controlling microscopic disseminated disease.

IMMUNOTHERAPY

Nonspecific Immunotherapy

In 1970s, nonspecific immunotherapy using BCG in various malignancies were reported. There have been six randomized clinical trials in lung cancer using percutaneous administration of BCG as postoperative adjuvant immunotherapy [35–40]. Most of the patients studied had Stages I and II disease, but the strain of BCG, dosage, method of administration, and schedule were varied in each series. The administration schedule of BCG ranged from a total of five doses to once weekly for 18 months and to every 2 weeks for 2 years. All but one series reported statistically significant superiority in survival of the treated patients (Table II).

There were some clinical observations of possible beneficial effects on survival of lung cancer patients who developed severe postoperative infection, such as empyema. This was speculated to be effects of host immunostimulation [41].

McKneally et al. reported their positive results of adjuvant immunotherapy with intrapleural BCG [42]. However, a subsequent randomized trial by the Lung Cancer Study Group failed to duplicate the positive results [43].

Systemic or local injection of killed Corynebacterium Parvum (C. Parvum), an anerobic organism, was found to have antitumor effects in experimental animal tumors.

Woodruff et al. [44] reported their results of Phase II randomized adjuvant therapy in 49 patients with resectable lung cancer using C. Parvum. Twenty-five patients postoperatively were given intravenous injection of C. Parvum. The survival of the treated patients appears to be superior to that of the no-treatment control.

The Ludwig Lung Cancer Study Group subsequently entered 475 patients with resectable lung cancer into a randomized postoperative adjuvant therapy study of intrapleural C. Parvum [45]. There was significant decrease in survival of the patients who received intrapleural C. Parvum.

OK-432 (Picibanil, Chugai Pharm. Co., Tokyo, Japan) was developed in Japan as an immunotherapeutic agent in malignant diseases. Watanabe et al. [46] reported results of adjuvant chemo-immunotherapy using OK-432. Postoperatively, OK-432 was given weekly, 2.0 units for over 3 years together with combination chemotherapy. A statistically significant improvement in the survival of the patients who received OK-432 was observed.

TABLE II. Adjuvant Therapy With BCG (Percutaneous) in Nonsmall-Cell Lung Cancer

Investigator	Year		Results
Pouillart et al. [35]	1977	60% 3 yr[a] 25% 3 yr[b]	} Effective in Stage I
Jansen et al. [36]	1978	31% 1 yr[a] 0% 1 yr[b]	} Effective
Mineo et al. [37]	1978	77% 2 yr[a] 38% 2 yr[b]	} Effective
Miyazawa et al. [38]	1979	100% 2 yr[a] 68% 2 yr[b]	} Effective
Millar et al. [39]	1980	24 mo Median[c] 33 mo Median[d] 27 mo Median[b]	} Not effective
Perlin et al. [40]	1980	72% 2 yr[a] 43% 2 yr[b]	} Effective in Stage I

[a]BCG.
[b]Control.
[c]Multiple punctures.
[d]Intradermal.

Trials of Levamisole

Levamisole was originally developed as an antiparasitic agent for cattle and later was found to have immunorestorative action. In the randomized clinical trial of adjuvant therapy with levamisole in 206 patients with lung cancer, by Amery et al. [47], 96 patients received 150 mg of levamisole for 3 days every 2 weeks for 2 years. The survival rate of the patients in the Levamisole group was better, but the difference was not statistically significant. Only when they compared the survival rate of 40 patients who received >80 mg/m^2 of Levamisole was statistically significant improvement in survival rate of the immunotherapy group noted [47].

Another trial of randomized adjuvant immunotherapy with levamisole by Van Houtte and associates [48] in 51 patients with Stage I and II lung carcinoma showed no effectiveness of the treatment. The dosage of levamisole, however, was different from that of Amery: 100 mg/m^2 twice weekly for 2 years was given after a course of adjuvant radiotherapy.

Specific Immunotherapy

Hollinshead et al. [49] in 1974 reported isolation of fractions of soluble human lung cancer cell surface antigens, which give delayed hypersensitivity skin reaction in lung cancer patients. These fractions were called lung cancer tumor-associated antigens (TAA). These TAAs cause cellular immune reaction to patients with lung cancer. Thus the TAA was used in clinical trials of specific immunotherapy.

A Phase II clinical trial of postoperative adjuvant tumor specific active immunotherapy of nonsmall-cell lung carcinomas using the TAA was conducted by Stewart et al. [50]. Postoperatively, the patients were divided into three groups: (1) control, (2) tumor vaccine (immunotherapy), and (3) methotrexate and tumor vaccine (chemo-immunotherapy).

Statistically significant improvement in the survival (78% at 5 years) of patients who received immunotherapy and/or chemo-immunotherapy was noted. The P value by Gehan's generalized Wilcoxon test was 0.001. Particularly, the survival of 13 patients who received chemo-immunotherapy was superior to that of 15 patients in the immunotherapy *alone* group. Subsequently, a prospective randomized clinical trial of adjuvant specific immunotherapy in Stages I and II squamous cell lung carcinoma was carried out [51].

Postoperatively, Stage I and II squamous lung carcinoma patients were randomized to three groups: Group I received followup only (conventional management); Group II received specific immunotherapy [complete Freund's adjuvant (CFA) + TAA]; and Group III received nonspecific immunotherapy (CFA only). Eighty-six patients were entered (of which 85 were evaluable).

For immunization (Group II) 0.25 ml of CFA was mixed with 500 micrograms of TAA and was injected intradermally three times at a monthly interval. The patients in Group III received CFA mixed with 0.25 ml of saline (instead of TAA). The lifetable 5-year survival of Group I was 34.5% (10/28 patients alive); Group II, 75% (19/25 patients); and that of Group III was 53.6% (15/28 patients) (Fig. 4). The median survival of the control group was 38 months, that of the specific immunotherapy group was 106 months, and that of nonspecific immunotherapy group was 71 months. The difference was statistically significant (P = .007).

The effectiveness of active specific immunotherapy given as an adjuvant therapy in squamous cell lung carcinoma was demonstrated by a randomized study. However,

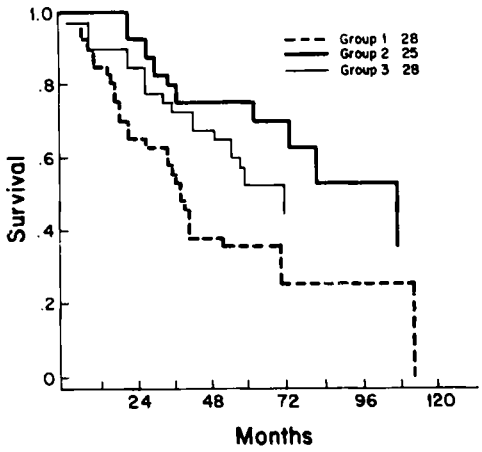

Fig. 4. Five-year survival rate for each of the treatment groups: Group 1 (Control), 34.5%; Group 2 (Specific Immunotherapy), 75%; Group 3 (Nonspecific Immunotherapy), 53.6% ($P = .007$). Used with permission of the Publisher, Wiley-Liss. Adapted from Journal of Surgical Oncology, Vol. 46, No. 1, January 1991, "Adjuvant, Specific, Active Immunotherapy for Resectable Squamous Cell Lung Carcinoma: A 5-Year Survival Analysis," by Takita et al. [51].

the study results were not well accepted because of relatively poor 5-year survival of the patients in the control group (34.5%). Also, characterization and identification of the lung cancer antigens are needed.

DISCUSSION

Preoperative radiation therapy was ineffective in improving the therapeutic results of surgery. Obviously, the explanation may be that most postoperative failure is at a distant site, whereas radiotherapy is a local treatment. Moreover, the postoperative morbidity and mortality rates are reported to be higher in patients who received preoperative radiotherapy.

Postoperative radiation therapy also was found to be ineffective in improving the survival. However, the Lung Cancer Study Group's clinical trial in Stages II and III epidermoid carcinoma showed a significant effect in controlling the local recurrence rate.

Study of the failure patterns following the surgical therapy of NSCLC revealed that approximately one-third was local recurrence and two-thirds were due to recurrence at distant sites. Logically then, systemic therapy such as chemotherapy, as adjuvant would produce better survival results. However, numerous trials of postoperative adjuvant chemotherapy showed no convincing effectiveness of this modality.

The reasons for failure of the postoperative adjuvant chemotherapy may be listed as follows:

1. The measurable lesions are removed by the surgery, and it is impossible to know the response of each patient to a given postoperative chemotherapy.
2. The surgical manipulation may cause the tumor to spread.
3. Postoperatively, chemotherapy may not be possible until at least 1 month after the surgery. It is known that tumor volume reduction is one of the stimuli for the tumor to grow.
4. Because of the surgery, tolerance to chemotherapy may be much lower than what it was preoperatively.
5. Compliance to the adjuvant therapy may not be good because the patient may feel falsely that he or she has already been cured by the surgery.
6. Past Phase III trials showed that only 53–68% of the patients in the adjuvant chemotherapeutic arm received the planned dose of chemotherapy.

In the area of neoadjuvant chemotherapy, we first reported in 1979 [20] that some unresectable NSCLC became resectable due to effective neoadjuvant chemotherapy. Since then, there were numerous laudable reports on Phase II neoadjuvant chemo(radio)-therapy in the successful downstaging of locally advanced borderline operable NSCLC (Stage IIIA). Finally, in 1994, Roth et al. [32] demonstrated by a prospective randomized study the superiority of neoadjuvant chemotherapy in IIIA NSCLC.

If neoadjuvant chemotherapy is found to be effective in Stage IIIA NSCLC, would it also be effective in resectable (Stages I and II) NSCLC?

The possible advantages of neoadjuvant chemotherapy are:

1. Response to chemotherapy would be measurable in each patient.
2. Possible tumor spread by surgical manipulation may be prevented by effective preoperative chemotherapy.
3. Chemotherapy is given at earliest possible time following diagnosis.
4. Tolerance to chemotherapy is much better, compared to the postsurgical status.
5. Better compliance to chemotherapy is expected because the tumor is not yet removed.

The 1970s was a decade for clinical trials for immunotherapy. Various nonspecific biological response modifiers (mostly BCG) were tested. Most of the investigators reported effectiveness of such treatments, but the results were not convincing. Presently, there is no evidence that authors who previously reported positive results have been pursuing the same subject of nonspecific immunotherapy.

We previously reported the effectiveness of adjuvant specific active immunotherapy of resectable NSCLC [51]. Since then, we planned further clinical trials, but they are on hold because we feel that further characterization of the TAA would be necessary.

From this review of the past results of perioperative adjuvant therapies, the author feels that the following should be investigated in the coming years to improve the results of surgical therapy of resectable NSCLC: (1) feasibility and efficacy of neoadjuvant chemotherapy for resectable (Stages I and II) NSCLC, (2) postoperative adjuvant specific active immunotherapy of resectable NSCLC using better characterized TAA.

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